REMARKS/ARGUMENTS

Status of the claims

Claims 1, 21-24, 27, and 29 are pending. Claims 2-20, 25, 26, 28, and 30-34 are withdrawn, as being drawn to non-elected inventions but joined by linking claim 1 (*see* November 1, 2005 Requirement for Restriction, page 3). Claims 35-48 are canceled.

Claim 1 is amended to make clear that the claimed invention is a chimeric construct which comprises a fusion protein comprising a targeting moiety that specifically recognizes a target microbial organism and an anti-microbial peptide. The dependent claims are amended to reflect the language of amended claim 1. Support for the amendments can be found, *e.g.*, on page 3, lines 7-11, page 4, lines 15-17, and Example 1, which describes design of a fusion protein. No new matter is added.

Priority

The Examiner has maintained the position that the priority application US Ser. No. 09/910,358 fails to provide support or enablement for one or more claims of the present application. While Applicants disagree with the Examiner's position, in an effort to expedite prosecution, Applicants address the references cited by the Examiner below. Applicants expressly reserve the right to revisit the priority issue at a later date, for example, in the event the claims are rejoined.

Objections to the claims

The Examiner objected to claims 1, 21-24, 27, and 29 as being drawn, in part, to non-elected inventions. The November 1, 2005 Requirement for Restriction states that claim 1 is a linking claim (*see* page 3). As explained in § 809 of the MPEP, once a linking claim directed to the elected invention is allowable, the restriction requirement between the linked inventions must be withdrawn. Thus, Applicants respectfully submit claims 1, 21-24, 27, and 29 as amended to await resolution of the outstanding rejections to linking claim 1.

Non-statutory obviousness-type double patenting

Claims 1, 21, 23, 27, and 29 were provisionally rejected for alleged non-statutory, obviousness-type double patenting over claim 20 of co-pending US Ser. No. 10/706,391, now allowed. Applicants will consider filing a terminal disclaimer upon an indication of otherwise patentable subject matter.

35 USC § 103(a)

Lehrer *et al.* in view of Goldenberg.

The rejection of claims 1, 21-24, 27, and 29 under 35 U.S.C. §103(a) as allegedly obvious in light of Lehrer *et al.* (U.S. Patent 6,492,328) in view of Goldenberg (U.S. Patent 5,332,567) was maintained. According to the Examiner, it would have been obvious for one of skill to use the antibody conjugate disclosed in Goldberg to deliver Novispirin G10 as disclosed by Lehrer. Applicants traverse by argument and amendment.

As reiterated by the Supreme Court in *KSR*, the framework for the objective analysis for determining obviousness under 35 U.S.C. 103 is stated in *Graham* v. *John Deere Co.* 383 U.S. 1, 148 USPQ 459 (1966). Obviousness is a question of law based on underlying factual inquiries. The factual inquiries enunciated by the Court are as follows:

(1) Determining the scope and content of the prior art;
(2) Ascertaining the differences between the claimed invention and the prior art; and
(3) Resolving the level of ordinary skill in the art.

However as recognized in the Examination Guidelines for Determining Obviousness Under 35 U.S.C. 103 in View of the Supreme Court Decision in *KSR International Co.* v. *Teleflex Inc.* Federal Register 72(195), at 5279:

> **When the prior art teaches away from combining certain known elements, discovery of successful means of combining them is more likely to be nonobvious**." [emphasis added]

Applicants explain below that when the scope and content of the prior art is properly considered, and the differences between the claimed invention and the priori art are properly ascertained, the prior art effectively teaches away from the presently claimed invention.

In the instant case, the pending claims are directed to:

> 1. A chimeric construct, said construct comprising a fusion protein wherein **a targeting moiety that specifically recognizes a target microbial organism is attached to an anti-microbial peptide**, and where said construct is specifically targeted to, and has an anti-microbial effect on the target microbial organism. [emphasis added]

In effect, the claims are directed to a chimeric construct where a broad-spectrum anti-microbial peptide is modified so that it "specifically recognizes a target microbial organism" and thereby loses its broad spectrum activity.

The cited art and other prior art, however teaches that:

1) Antimicrobial peptides have broad spectrum activity; and

2) Broad spectrum activity **is a desirable feature** in antimicrobial peptides.

For example, Hancock and Scott (2000) *Proc. Natl. Acad. Sci., USA*, 97(16): 8856-8861 (a copy of which is provided herewith) teaches:

> Cationic antimicrobial peptides **have many of the desirable features of a novel antibiotic class** (6). **In particular, they have a broad spectrum of activity,** kill bacterial rapidly, are unaffected by classical antibiotic resistance mutations, do not easily select antibiotic resistant variants, show synergy with classical antibiotics, neutralize endotoxin, and are active in animal models. [emphasis added] (*see,* p 8860, col. 2)

Similarly, Gottleib *et al.* (2008) *BMC Microbiology*, 8: 205 (provided herewith) teaches

> Indeed, several novel HDPs have been discovered and are thought to represent one of the most innovative families of anti-infective agents that have been characterized over the last 25 years [4,5]. In addition, HDPs have also been suggested as natural alternatives to chemical food preservatives [39-41].

> Our data indicate that such host defense peptides would be **well suited for both purposes as they appeared to have broad bactericidal effect** on human pathogenic bacteria with different expression patterns of virulence factors. [emphasis added] (page 9)

while Marshall and Arenas (2003) *Electron. J. Biotechnol.*, 6(2): 271-284 (provided herewith) teaches the desirability of even broadening the activity spectrum of antimicrobial peptides:

> A resulting new generation of anti microbial peptides (AMPs) with higher specific activity and **wider microbe-range of action** could be constructed, and hopefully endogenously expressed in genetically-modified organisms. [emphasis added] (*see* abstract).

Even Lehrer *et al* cited by the Examiner pertaining to antimicrobial peptides impliedly teaches the desirability of broad spectrum antimicrobial activity in antimicrobial peptides. In particular, Lehere *et al.* for example teaches the desirability of antimicrobial activity against gram negative bacteria:

> There is a clinical need for novel antibiotic agents **that are active against drug resistant Gram-negative bacteria**, and which have low toxicity against mammalian cells. [emphasis added] (col. 2, lines 6-9)
> * * *
>
> Methods and compositions are provided for the use of novispirin peptides. Novispirin peptides are small antimicrobial agents with potent activity against **Gram-negative bacteria, including Chlamydia trachomatis, Pseudomonas aeruginosa, Eschelichia coli and Stenotrophomonas maltophilia**. (col. 2, lines 20-25)

In this regard, it is noted that gram negative bacteria comprise a large group including, but not limited to *Escherichia coli*, *Salmonella*, *Shigella*, various Enterobacteriaceae, *Pseudomonas*, *Moraxella*, *Helicobacter*, *Stenotrophomonas*, *Bdellovibrio*, *Legionella* alpha-proteobacteria including *Wolbachia* and many others, cyanobacteria, spirochaetes, *Neisseria gonorrhoeae*, *Neisseria meningitidis*, *Moraxella catarrhalis*, *Hemophilus influenzae*, *Klebsiella*

pneumoniae, *Legionella pneumophila*, *Pseudomonas aeruginosa*, *Escherichia coli*, *Proteus mirabilis*, *Enterobacter cloacae*, *Serratia marcescens*, *Helicobacter pylori*, *Salmonella enteritidis*, *Salmonella typhi*, *Acinetobacter baumannii*, and the like.

Goldenberg, cited by the Examiner, offers no teaching whatsoever regarding antimicrobial peptides. Moreover, this reference teaches the use of targeted antibiotics to reduce systemic toxicity. In contrast to the antibiotics contemplated by Goldenberg (*e.g.*, tracyclines, chloramphenicol, piperazine, chloroquine, diaminopyridines, metroniazide, ietc. (see col. 16, lines 46-53)), many antimicrobial peptides are naturally produced in mammals and show **low toxicity against mammalian** cells. Accordingly the motivation to target antimicrobials found in Goldenberg is far less applicable to antimicrobial peptides, **particularly in view of the general view in the art that broad spectrum antimicrobial peptides are desired**.

In view of the foregoing, it is clear that:

Graham Factor 1: The scope and content of the prior art teaches that antimicrobial peptides are broad spectrum of activity and **such broad spectrum activity is desired**; and

Graham Factor 2: One difference between the claimed invention and the prior art is the modification of an antimicrobial peptide so that it **no longer** possesses broad spectrum and instead, recognizes a target microbial organism.

Graham Factor 3: The level of skill in the art is high (typically Ph.D.). However the prior art that teaches the desirability of broad spectrum activity of antimicrobial peptides is created by those of skill in the art.

Thus, when the scope and content of the prior art is properly considered, and the differences between the claimed invention, and the prior art are properly ascertained, and the level of skill in the art is considered, the prior art effectively teaches away from the presently claimed invention. Accordingly the Examiner has failed to make his *prima facie* case under 35 U.S.C. §103(a) and the rejection of claims 1, 21-24, 27, and 29 under 35 U.S.C. §103(a) in light of Lehrer *et al.* and Goldenberg should be withdrawn.

Lehrer *et al.* in view of Shi

The Examiner maintained the rejection of claims 1, 21-24, 27, and 29 as allegedly obvious in light of Lehrer *et al.* (supra) in view of Shi *et al.* (US Patent Application Publ. No. 2004/0052814, "Shi '814"). Applicants traverse.

Applicants submit herewith Declaration under 37 CFR 1.132 stating that Shi '814 and the present application were subject to an obligation to assign to the same organization at the time the present invention was made. As explained in § 706.02(l)(2) of the MPEP, such evidence is generally considered sufficient to disqualify a cited reference as prior art.

As explained previously, Lehrer discloses only that Novispirin G10 is useful for killing *Pseudomonas aeruginosa*. Moreover, as explained above, the prior art, when considered as a whole, teaches that antimicrobial peptides have broad-spectrum activity and that such activity is desirable. The prior art thus effectively leads one of skill away from modifying Novispirin G10 (or other AMPs) to reduce or eliminate their broad spectrum activity.

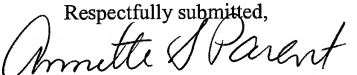
Accordingly the Examiner has failed to make his *prima facie* case under 35 U.S.C. §103(a) and the rejection of claims 1, 21-24, 27, and 29 under 35 U.S.C. §103(a) in light of Lehrer *et al.* and Goldenberg should be withdrawn.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance and an action to that end is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,



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